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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,407	TORRANCE ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *21-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-52 are pending. Claims 21-52 remain withdrawn form consideration. Claims 1-20 are under consideration.

Sections of text of Title 35 US Code not found in this action can be found in a prior action.

The rejection of claims 1-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-17 are drawn to a genus of isogenic cell lines comprising a "gene of interest". The claims are relying upon the identity of said gene of interest in order to characterize the claimed cell lines. The genes of interest encompass any allele of any gene, including mutant, and null alleles. the specification describes the isogenic cell lines wherein the first cell is heterozygous comprising a wt Ras gene and a mutant Ras gene, and wherein the second cell is hemizygous for wild-type Ras. The art recognizes the sequences of numerous mutations of Ras which are found in human tumor specimens and which confer a tumorigenic phenotype when transfected into host cells. The genus comprising "genes of interest" encompasses any gene beyond the scope of the described Ras genes, and includes tumor suppressor genes, and genes not related to cancer cells or the tumorigenic phenotype. the description of the Ras oncogenes does not describe the genus of "genes of interest" on which the instant claims for isogenic cell lines depend because the genus is highly variant encompassing genes, such as tumor suppressor genes, which differ from the Ras oncogenes in that said genes are recessive and not dominant-negative, in addition to genes which are not related to cancer cells or the tumorigenic phenotype.

Further, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d

1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

In the instant claims, the genus is described only as genes of interest are not limited either by function or by structure.

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A cell line comprising a gene wherein the gene is not adequately described a cannot itself be adequately described..

Thus, the instant specification may provide an adequate written description of isogenic cell lines comprising mutant Ras genes, per Lilly if the claims were limited to such. however, at present the claims have no limitation as to functional attributes, as per Enzo, nor does the specification describe a number of specific examples that would adequately describe the highly variant genus. Thus, one of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus of isogenic cells because applicant did not adequately describe the genus of "genes of interest".

Applicant argues that based on the written description requirement, the specification need describe in detail only that which is "new of not conventional in the art". The examiner agrees with that point. However, that is not the fact pattern in the instant application. The claims under rejection for lacking adequate written description are drawn to a first and second cell wherein the first cell and the second cell are isogenic but for a gene of interest and a gene encoding a fluorescent protein. Genes encoding fluorescent proteins are conventional in the art and do not require a detailed written description. However a pair of isogenic cells comprising a gene of interest are not conventional in the art as evidenced by the rejections under 35 USC 103(a) rather than 35 USC 102(b). Therefore it can be concluded that the instant pair of cells are new and unconventional in the art. For the reasons stated in the original rejection, applicant has failed to describe a representative number of said cells because only one pair of cells has been described, or describe the pair of cells in such a way as to link a partial structural characterization with the functional of the single pair of cells which where described. Applicant's argument regarding the usage of "gene of interest" in the art is not persuasive to overcome the written description rejection for the original reasons set forth. Applicants argument regarding US 6,376,175 is unpersuasive because US 6,376,175 is not being examined, 09/961,407 is being examined. Applicant's arguments that they are not claiming a new gene of interest is unpersuasive because

the genus of "gene of interest" comprises new genes and cannot be construed to be limited to only those previously described genes. Further, applicant's claim that they are not claiming new genes or interest is incorrect, because in order to make the isogenic cell lines, one of the cells must contain a mutated "gene of interest". Said mutated "gene of interest" is the core of the invention as this is the altered gene that makes the pair of cells an isogenic pair of cells.

The rejection of claims 1-17 over Waldman (US 2002/0132340, priority to 60/274,393) in view of Kain (Drug discovery today, 1999, vol. 4, pp. 304-312) is maintained for reasons of record..

Claim 1 is drawn to a pair of cells comprising a first cell and a second cell wherein the first cell and the second cell are isogenic but for a gene of interest and a gene encoding a fluorescent protein; wherein the first cell comprises a gene that encodes a first fluorescence protein having an absorption spectrum and a first emission spectrum; wherein the second cell comprises a gene that encodes a second fluorescent protein having a second absorption spectrum and a second emission spectrum, and wherein either the first and second absorption spectra are not identical and/or the first and second emission spectra are not identical. claim 2 embodies the pair of cells of claim 1 wherein the first and second absorption spectra are not identical and the first and second emission spectrum are not identical. Claim 3 embodies the pair of cells of claim 1 wherein the cells are contained within the same undivided container. Claim 4 embodies the pair of cells of claim 1 wherein the first cell is homozygously wild-type for the gene of interest and wherein the second cells is homozygoulsy mutant for the gene of interest. Claim 5 embodies the pair of cells of claim 1 wherein the gene of interest in the second cell is homozygously deleted. Claim 6 embodies the pair of cells of claim 1 wherein the first cell comprises two wild-type alleles of the gene of interest, and wherein the second cell comprises a wild-type allele and a mutant allele of the gene of interest wherein the mutant allele is dominant. Claim 7 embodies the pair of cells of claim 1 wherein the gene of interest is an oncogene and the first cell is homozygous for a mutant allele of the oncogene and wherein the second cell comprises a homozygous deletion of the mutant oncogene. Claim 8 embodies the pair of cells of claim 1 wherein the first cell expresses the gene of interest and wherein the second cell does not express the gene of interest. Claim 9 embodies the pair of cells of claim 1 wherein the first cell

comprises a wild-type allele and a mutant allele of the gene of interest and the second cell is hemizygous for the wild-type allele of interest. Claim 10 embodies the pair of cells of claim 1 wherein the first cell expresses a protein encoded by the gene of interest and wherein the second cell does not express a protein encoded by the gene of interest. Claims 11 and 12 embody the pair of cells of claim 1 wherein the first and second cells are mammalian cells and human cells, respectively. Claims 15 and 16 specify that the cells of claim 1 are HCT116 cells and DLD-1 cells, respectively. Claim 17 embodies the pair of cells of claim 1 wherein the first and second fluorescent protein are selected from the group consisting of green , red, blue, yellow and cyan fluorescence protein. Claim 13 embodies the pair of cell of claim 1 wherein the cells are cancer cells. Claim 14 embodies the pair of cells of claim 13 wherein the cancer cells are selected from the group consisting of colon tumor cells and breast tumor cells.

Waldman teaches a pair of isogenic cell lines comprising beta-catenin, wherein said cells are heterozygous for a wild-type and a mutant beta catenin gene, or hemizygous for wild-type beta-catenin, hemizygous for mutant beta-catenin, homozygous for wild-type beta catenin and homozygous for mutant beta-catenin [0010-0012]. It is noted that the descriptions of first and second cells by Waldman et al is not limiting and done only for descriptive purposes [0032]. Waldman teaches that the pair of cells can include cells which are null for beta-catenin expression, thus fulfilling the specific embodiment of claims 8 and 10, drawn to the second cell not expressing the gene of interest or the protein of the gene of interest. Waldman defines "hemizygous" as cells containing only a single copy of the beta-catenin gene or a single functional beta-catenin gene [0034]. Waldman teaches a method wherein a therapeutic agent is identified that allows for the selective killing of cells expressing mutant beta-catenin but not wild-type beta catenin comprising contacting an isogenic set of cells with a test agent and identifying an agent that allows for the selective killing [0020]. Waldman teaches that the set of isogenic cell lines can be prepared from human colon carcinoma cells of the HCT-116 cell line and the DLD-1 cell line [0038-0039], thus fulfilling the specific embodiments of claims 11-16. Waldman teaches that the isogenic cell line disclosed represents an improvement over the prior art because they make possible a method for distinguishing between a compounds which selectively kills cancer cells having mutant rather than wild-type beta catenin and compounds which kill cells but re not selective for cells having mutant rather than wild-type beta catenin

[0029]. Waldman teaches that a polypeptide expressed from a polynucleotide of a recombinant nucleic acid can confer a detectable phenotype on the cell, and the detectable phenotype can be used as a surrogate for increased resistance or susceptibility to a toxic agent, and that the detectable phenotype can include the production of a fluorescent signal [0047]. Waldman teaches that red, green and cyan fluorescent proteins as specific embodiments of fluorescent proteins which can act as reporter molecules [0048]. Waldman does not teach a fluorescent gene incorporated into the first cell and the second cell wherein said fluorescence genes encoded proteins having different emission and excitation spectra.

Kain teaches the use of multicolored florescent proteins for more detailed information regarding cellular processes (page 310, first column, lines 3-5) and teaches the use of fluorescent proteins are reporter for transcription (page 306, second column). Kain teaches various fluorescent proteins which have different excitation and emission maxima (page 306, Table 1) thus fulfilling the limitations of claims 1 and 17. Kain teaches that various combinations of the disclosed fluorescent proteins have been used to quantify mixed cell populations (page 306, first column, lines 29-32)

It would have been prima facie obvious to one of skill in the art at the time the invention was made to make the isogenic cells expressing the beta catenin wild type and mutant alleles, wherein said mutant alleles were fused to a fluorescent protein and wherein a wild-type allele was fused to a different fluorescent protein than the mutant allele. One of skill in the art would be motivated to do so in order to use the color of the fluorescent protein as a detectable phenotype of the cell in order to measure the effects of toxic agent on said cell as taught by Waldman et al. One of skill in the art would be motivated to do so because Waldman suggests the use of a fluorescent signal as a detectable phenotype. One of skill in the art would known that a mixture of cells expressing wild type and mutant alleles of beta catenin can be more effectively assayed in a screen if the control wild type cells are exposed to the exact same conditions of the assay as the cells containing mutant, truncated or otherwise abnormal alleles of beta catenin and that co-culture would enable the cells to be subject to the same microenvironment. One of skill in the art would know that in order to discern between a signal from a mutant allele and a signal from a wild-type allele, a different color of fluorescent label should be used which ideally would have a different excitation maximum and a different

emission spectrum so that spectra from the mutant allele can be generated from a separate excitation wavelength than the wild-type allele and the subsequent emission spectrum can be measured.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the asserted motivation is insufficient for one of ordinary skill n the art to have combined the cited references and that the teachings of the cited references must be combined as a whole and compared with the subject matter of the rejected claims (THIS HAS TO DO WITH TEACHING AGAINST). This has been considered but not found persuasive. When combined as a whole there is nothing in the individual references which would "teach against" the combination. Applicant argues that the general teachings of the references be looked at to the extent that the specific technical teachings be ignored. This is not persuasive or permitted in patent examination. It is noted that the general skill of the routineer is high when considered the filing date of the instant application. It is a routine matter for one of ordinary skill in the art to use reporter constructs to monitor cellular activity. This is corroborated by the teachings of Waldman et al in paragraph [0048] as set forth on page 5 of the instant office action. Applicant argues that Waldman et al does not teach or suggest the use of isogenic cell lines containing two distinguishing molecules (the "gene of interest", the same that applicant argues above to be conventional in the art). Applicant argues that Waldman defines a pair of isogenic cell lines as "at least two separate populations of cells that are substantially genetically identical except for the nucleotide sequence of their B-catenin genes" and somehow that this does not

apply to the instant invention because the set of isogenic cell lines described by Waldman are separate cell lines. This has been considered but not found persuasive. Applicant is reminded that the rejection was mad as a 103 and not a 102. The motivation for combining the cells would be obvious in the light of the teachings of Kain on the various combinations of green fluorescent protein mutants which can be used to quantify mixed cell populations by flow cytometry. Applicants arguments that there is insufficient motivation to combine is unpersuasive because Waldman does not specifically teach a mixed population of cells. One of skill in the art would know that testing a mixed population of cells is advantageous to testing two separate groups of cells because "One of skill in the art would known that a mixture of cells expressing wild type and mutant alleles of beta catenin can be more effectively assayed in a screen if the control wild type cells are exposed to the exact same conditions of the assay as the cells containing mutant, truncated or otherwise abnormal alleles of beta catenin and that co-culture would enable the cells to be subject to the same microenvironment. One of skill in the art would know that in order to discern between a signal from a mutant allele and a signal from a wild-type allele, a different color of fluorescent label should be used which ideally would have a different excitation maximum and a different emission spectrum so that spectra from the mutant allele can be generated from a separate excitation wavelength than the wild-type allele and the subsequent emission spectrum can be measured".

The rejection of claims 1-3, 11-20 over Shirasawa et al (Science, 1993, vol. 260, pp. 85-88) in view of Vande Woude et al (U.S. 5,645,988) and Kain (Drug Discovery Today, 1999, vol. 4, pp. 304-312) is maintained for reasons of record.

The specific embodiments of claims 1-3 and 11-17 are set forth above.

Claim 18 embodies the method of claim 1 wherein the gene of interest is Ras and wherein the Ras genotype of the first cell is c-Ki-Ras (Wt/Mut), and wherein the Ras genotype of the second cell is c-Ki-Ras(WT/Null).

Claim 19 is drawn to a pair of cells comprising a first cell wherein the Ras genotype of the first cell is c-Ki-Ras (WT/mut) and wherein the first cell comprises a first gene that encodes a first fluorescent protein having a first absorption spectrum and a first emission spectrum and a second cell wherein the Ras genotype of the second cell is c-Ki-Ras(Wt/null) wherein the second

cell comprises a second gene that encodes a second fluorescent protein having a second absorption spectrum and a second emission spectrum that is nor identical to the first emission spectrum, wherein said first and said second cells are isogenic but for the Ras gene, and the gene encoding a fluorescent protein. Claim 20 embodies the pair of cells of claim 19 wherein the first fluorescent protein is blue and the second fluorescent protein is yellow fluorescent protein..

Shirasawa et al teach that point mutations which activate wild-type ki-Ras to oncogenic Ki-Ras are present in about 50% of human colorectal tumors (abstract). Shirasawa et al teach the targeting of the mutant ki-Ras gene for a homologous recombination event with a vector having a interrupted Ras gene sequence. Shirasawa et al teach that for DLD-1 colon cancer cells, three of the clones were disrupted at the mutant allele and four were disrupted at the normal allele (page 85, third column, lines 27-31) and in HCT-116 cells three of the clones were disrupted at the mutant K-ras allele and five were disrupted at the normal K-Ras allele (page 87, first column, lines 6-11). Thus, the clones which were disrupted at the mutant K-ras allele are the same as the c-Ki-Ras (WT/null) genotype of the second cell and the starting DLD-1 and HCT-116 cells are Ki-Ras (WT/mut). Shirasawa et al teach that the only distinction between the parental cell lines and the cell lines comprising disrupted mutant K-ras alleles is the expression of the mutated K-ras genes. Shirasawa et al do not teach the isogenic cells which additionally express two fluorescent proteins which differ by emission spectrum and excitation spectrum.

Vander Woude et al teach cancer cells derived from the same type of biological material wherein the cancer cells differ as to the presence of a particular DNA sequence (column 11, lines 27-30) wherein the preferred DNA sequence is K-ras-2 which has been activated by a mutation in the 12th, 16th or 61st codon (column 12, lines 1-4). Vande Woude et al teach the desirability of selecting drugs which specifically target oncogenes (column 5, lines 9-14, column 8, lines 57-65) which includes Ras oncogenes (column 14, lines 28-32). Vande Woude et al do not teach pairs of isogenic cells.

Kain teaches the use of multicolored florescent proteins for more detailed information regarding cellular processes (page 310, first column, lines 3-5) and teaches the use of fluorescent proteins are reporter for transcription (page 306, second column). Kain teaches various fluorescent proteins which have different excitation and emission maxima (page 306, Table 1) thus fulfilling the limitations of claims 1 and 17. Kain teaches that various combinations of the

disclosed fluorescent proteins have been used to quantify mixed cell populations (page 306, first column, lines 29-32).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to make the isogenic cells as taught by Shirasawa et al with the exception that the isogenic cells included a gene encoding a first fluorescent protein attached to the mutant ras allele and a second fluorescent protein attached to the disrupted ras allele, wherein the first fluorescent protein is blue and the second fluorescent protein is yellow. One of skill in the art would be motivated to do so in order to use the color of the fluorescent protein as a detectable phenotype of the cell in order to measure the effects of toxic agent on cell which comprise the oncogenic Ras mutations as taught by Vander Woude et al. One of skill in the art would known that a mixture of cells expressing the activated oncogenic ki-Ras protein and the disrupted ki-Ras protein can be more effectively assayed in a screen if both the first and the second cells are exposed to the exact same conditions of the assay which would be fulfilled by the co-culture of said cells within the same undivided culture dish. One of skill in the art would know that in order to discern between a signal from a mutant allele and a signal from a wild-type allele, a different color of fluorescent label should be used which ideally would have a different excitation maximum and a different emission spectrum so that spectra from the mutant allele can be generated from a separate excitation wavelength than the wild-type allele and the subsequent emission spectrum can be measured. One of skill in the art would know that the greater the separation between the excitation maxima of the first and second fluorescent proteins, the greater the probability that a fluorescent protein emission can be observed separately for each of the first and second fluorescent proteins. Based on this reasoning, it would have been obvious to select EBFP (blue) having an excitation maximum of 380 nm and EYFB (yellow) having an excitation maximum of 513 nm, thus fulfilling the specific embodiment of claim 20.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Again, applicant argues that when the entire teachings of the cited references are considered , there exist no legally sufficient motivation for on of ordinary skill in the art to have combined the cited teachings. Applicant somehow reasons that one of skill in the art should ignore specific technical information taught by each of the references and just look at each of the references as a whole. This has been considered but not found persuasive. One of skill in the art would be motivated to combine the teachings in order to make technical advances, legally sufficient motivation is irrelevant to those who are routineers. Applicant argues that the cell lines containing the disrupted ki-ras genes as taught by Shirasawa et al (DLD-1 and HCT-116, the same as that of instant claims 15 and 16) but that there exists no teachings in Shirasawa et al that said cell lines could be used to screen for toxic agents or that it would be useful to incorporate a fluorescent marker. Applicant quotes Shirasawa et al "Thus, the use of these cell lines in studies of oncogene and tumor suppressor genes cooperation may help elucidate further the molecular mechanisms that underlie colorectal mutagenesis". This has been considered but not found persuasive. Shirasawa et al obviously teach using the cell lines to investigate oncogenesis. In this mode, one of skill in the art would easily envision screening the cell lines with agents that would cause the cell lines comprising activated ki-Ras to exhibit a malignant phenotype. In light of the teaching of Vande Woude et al on the desirability of selective drugs which specifically target oncogenes, especially Ras oncogenes. With regard to applicants argument regarding the teachings of Kain et al, it is noted that one of skill in the art would immediately recognize the advantage of monitoring a mixed population of cells because "One of skill in the art would known that a mixture of cells expressing the activated oncogenic ki-Ras protein and the disrupted ki-Ras protein can be more effectively assayed in a screen if both the first and the second cells are exposed to the exact same conditions of the assay which would be fulfilled by the co-culture of said cells within the same undivided culture dish. One of skill in

the art would know that in order to discern between a signal from a mutant allele and a signal from a wild-type allele, a different color of fluorescent label should be used which ideally would have a different excitation maximum and a different emission spectrum so that spectra from the mutant allele can be generated from a separate excitation wavelength than the wild-type allele and the subsequent emission spectrum can be measured. One of skill in the art would know that the greater the separation between the excitation maxima of the first and second fluorescent proteins, the greater the probability that a fluorescent protein emission can be observed separately for each of the first and second fluorescent proteins. Based on this reasoning, it would have been obvious to select EBFP (blue) having an excitation maximum of 380 nm and EYFB (yellow) having an excitation maximum of 513 nm, thus fulfilling the specific embodiment of claim 20.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/27/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER